REMARKS

The Office Action

Claims 12-15, and 19-28 were pending in this application. With this reply claims 29 and 30 have been added. Claims 12, 13, 15, and 19-23 stand rejected under 35 U.S.C. § 102(b). Claims 12, 13, 15, and 19-23 stand further rejected under 35 U.S.C. § 103. Applicant addresses these rejections with the following remarks.

Rejection under 35 U.S.C. ə 102(b)

Claims 12, 13, 15, and 19-23 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Zhang et al., J. Pharm. Sci. 2001 (hereafter "Zhang"). Applicant has addressed this rejection by amendment of claim 12 and with the following arguments.

Applicant notes that as amended claim 12, and dependent claims 13-15 and 19-30, now include the limitation that the corticosteroid conjugate is resistant to *in vivo* cleavage.

Zhang teaches the use of a corticosteroid-dextran prodrug conjugate for the treatment of inflammatory conditions. See, for example, Zhang at page 2079, right column, which recites:

> Dextran-methyprednisolone succinate (DMP), a conjugate of MP and dextran containing two ester bonds, was synthesized using succinic acid as a linker between the polymer and MP (Scheme 1). Hydrolysis studies showed that at physiological pH, DMP is slowly hydrolyzed at both ester bonds (Scheme 1), resulting in the formation of MP and methylprednisolone succinate (MPS), the latter being subsequently converted to MP.

The corticosteroid conjugate of Zhang is designed to be cleaved *in vivo*. The purpose of the Zhang's conjugate is to target the corticosteroid to the liver and spleen. Once delivered to the targeted site, the conjugate is cleaved, releasing unconjugated corticosteroid at the site. See, for example, Zhang in the abstract, which recites:

> As for tissue distribution, the conjugate delivered the steroid primarily to the spleen and liver as indicated by 19- and 3-fold increases, respectively, in the tissue/plasma area under the curve (AUC) ratios of the steroid. On the other hand, the tissue/plasma AUC ratios of

> the prodrug in other organs were negligible. Active MP was released from DMP slowly in the spleen and liver, and AUCs of the regenerated MP in these tissues were 55- and 4.8-fold, respectively, higher than those after the administration of the parent drug.

In contrast to Zhang, the claims of the present invention are directed to the use of corticosteroid conjugates that are resistant to *in vivo* cleavage. See, for example, the specification at page 21, lines 15-22, which recite:

> The corticosteroid conjugates of the present invention are designed to largely remain intact in vivo, resisting cleavage by intracellular and extracellular enzymes (e.g., amidases, esterases, and phosphatases). Any in vivo cleavage of the corticosteroid conjugate produces the parent steroid, resulting in the unnecessary and potentially harmful exposure of the central nervous system to this corticosteroid. Thus, the corticosteroid conjugates of the invention are not prodrugs, but are therapeutically active in their conjugated form, resulting in an improved therapeutic index relative to their parent, unconjugated, corticosteroid.

All of the pending claims are directed to corticosteroid conjugates that are resistant to *in vivo* cleavage. Because Zhang teaches the use of corticosteroid conjugate prodrugs which undergo cleavage *in vivo*, Zhang is not relevant to the novelty of the pending claims.

In view of the amendment to claim 12 and the arguments above, Applicant requests withdrawal of the rejection for lack of novelty.

Rejection under 35 U.S.C. ə 103(a)

Claims 12, 13, 15, and 19-23 stand rejected under 35 U.S.C. § 103 for obviousness over Zhang. Applicant has addressed this rejection by amendment of claim 12 and with the following arguments.

To establish a *prima facie* case of obviousness, the prior art reference(s) must teach or suggest all of the claim limitations, there must be some motivation or suggestion to modify the prior art reference, and there must be a reasonable expectation of success. MPEP 2143.

As amended, all of the pending claims are directed to corticosteroid conjugates

that are resistant to *in vivo* cleavage. Zhang teaches only the use of cleavable prodrug corticosteroid conjugates, i.e. conjugates that are not resistant to *in vivo* cleavage.

All of the pending claims are nonobvious over Zhang because Zhang does not teach or suggest the use corticosteroid conjugates resistant to *in vivo* cleavage for the treatment of autoimmune or inflammatory conditions. This limitation is missing from the prior art cited by the examiner.

In view of the amendment to claim 12 and the arguments above, Applicant requests withdrawal of the rejection for obviousness.

Support for the Amendment to claim 12

All of the pending claims, claims have been amended to include the limitation that the corticosteroid conjugate is "resistant to *in vivo* cleavage." Support for this limitation is found in the specification at page 10, lines 3-5, and at page 21, lines 15-22. No new matter has been added with this amendment.

Support for new claim 29 and 30, which are directed to corticosteroid conjugates including bulky groups above 600 and 800 daltons, respectively, is found in the specification at page 19, lines 5-10.

CONCLUSION

Applicants submit that the claims are now in condition for allowance and such action is respectfully requested. To expedite prosecution applicants request a telephonic interview with the Examiner to discuss any remaining rejections. The Examiner is invited to call the undersigned at 617-428-0200.

Enclosed is a Petition to extend the period for replying to the Office action for 3 months, to and including September 30, 2005, and a check in payment of the required extension fee.

Also enclosed is a check for $50.00 for the two new dependent claims. If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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